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(54) Title: NOVEL COMPOUNDS FOR THE TREATMENT OF SICKLE CELL DISEASE

(57) Abstract: Compounds have been designed to inhibit the action of cytochrome b5 in the physiological re-reduction of auto-oxidized hemoglobin (methemoglobin), for the purpose of increasing methemoglobin levels in the blood of patients as a treatment for sickle cell disease. Administration of the compounds mimics congenital deficiencies in cytochrome b5, in which methemoglobin levels rise as high as 50% of total hemoglobin and derivatives in the blood, without adverse clinical manifestations. Methemoglobin inhibits red cell sickling and high levels of methemoglobin in the blood induced by the compounds of this invention prevent the symptoms of sickle cell disease.

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# INTERNATIONAL SEARCH REPORT

PCT/US2004/002543

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07G17/00 C07H19/00 C07H19/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07G C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HOSSEINI M W ET AL: "MULTIPLE MOLECULAR RECOGNITION AND CATALYSIS. A MULTIFUNCTIONAL ANION RECEPTOR BEARING AN ANION BINDING SITE, AN INTERCALATING GROUP, AND A CATALYTIC SITE FOR NUCLEOTIDE BINDING AND HYDROLYSIS"</p> <p>1990, JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, PAGE(S) 3896-3904 , XP000891840</p> <p>ISSN: 0002-7863</p> <p>figures 9,10</p> <p style="text-align: center;">----- -/--</p>	11

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

29 June 2004

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23/08/2004

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# INTERNATIONAL SEARCH REPORT

PCT/US2004/002543

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LOMOZIK, LECHOSLAW ET AL: "Copper(II) ions as a factor interfering in the interaction between bioligands in systems with adenosine and polyamines" 1996, JOURNAL OF INORGANIC BIOCHEMISTRY , 63(3), 191-206 CODEN: JIBIDJ; ISSN: 0162-0134 , XP002286291	11
A	FENNIRI, HICHAM ET AL: "Molecular recognition of NADP(H) and ATP by macrocyclic polyamines bearing acridine groups" HELVETICA CHIMICA ACTA , 80(3), 786-803 CODEN: HCACAV; ISSN: 0018-019X, 1997, XP001189678	11
A	POL'SHAKOV, V. I. ET AL: "Interaction of the antitumor drugs prospidin and spirobromin with nucleotides" KHIMIKO-FARMATSEVTICHESKII ZHURNAL , 21(5), 528-36 CODEN: KHFZAN; ISSN: 0023-1134, 1987, XP009032761	11
A	POL'SHAKOV, V. I. ET AL: "Interaction of spirazidine, prospidine, and spirobromine with nucleic acid components" KHIMIKO-FARMATSEVTICHESKII ZHURNAL , 23(1), 10-16 CODEN: KHFZAN; ISSN: 0023-1134, 1989, XP009032762	11

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-10,12-23

Present claims 1-10, 12-23 relate to a compounds defined by reference to a desirable characteristic or property, namely compounds "that bind to the hemoglobin binding site on cytochrome b5 and competitively inhibits hemoglobin binding to cytochrome b5"

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed; namely those parts relating to the compounds having the following simultaneous characteristics :

Compounds wherein

- 1) R1 is defined as in claims 2-4 (a linear or cyclic polyamine or hexacyclene) and
- 2) R2 is a moiety that links R1 and R3 (whatever this moiety may represent) and
- 2) R3 is defined as in claims 7-9 (ATP or ATP analogues).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

PCT/US2004/002543

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-10, 12-23  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.